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EXAMINER	
PORTNER, VIRGINIA ALLEN	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/506,749	CUTTING, SIMON MICHAEL	
	Examiner	Art Unit	
	Ginny Portner	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 July 0529*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32-37,39-54,57-73 and 75-79* is/are pending in the application.

4a) Of the above claim(s) *49,52,53 and 75-79* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-37,39-48,50,51,54 and 57-73* is/are rejected.

7)☒ Claim(s) *32-35,37,43-44,60-61* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/2006;8/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *See Continuation Sheet*.

Continuation of Attachment(s) 6). Other: addition pages requesting original support for amendments.

DETAILED ACTION

Claims 32-37, 39-54, 57-73, 75-79 are pending.

Claims 32-27, 39-54, 57-73 are under consideration.

Claims 49 (non-elected species OppA), 52-53 (cytoplasmic vegetative cell protein) and 75-79 stand withdrawn.

Election/Restrictions

1. Applicant's election with traverse of Group I, claims 32-37, 39-54, 57-73 in the reply filed on May 29, 2007 is acknowledged. The traversal is on the ground(s) that Groups I and III relate to a single general inventive concept and the spores of Group I, represent a linking general inventive concept and should be examined together. Applicant elects the species of antigen Tetanus Toxin C and the rrnO gene.

1. This is not found persuasive because WO 02/00232 (reference of record in International Search Report) describes the claimed special technical feature, thus not defining a unifying special technical feature that makes a contribution over the prior art.

2. The requirement is still deemed proper and is therefore made FINAL.

3. Because these inventions are independent or distinct for the reasons given above and there would be a serious burden on the examiner if restriction is not required because the inventions have acquired a separate status in the art in view of their different classification, restriction for examination purposes as indicated is proper.

4. Group I, Claims 49, 52-53 and Group III claims 75-79 are directed non-elected inventions (species and group, respectively).

5. The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and the product claims are subsequently found allowable, withdrawn process claims that depend from or otherwise require all the limitations of the allowable product claim will be considered for rejoinder. All claims directed to a nonelected process invention must require all the limitations of an allowable product claim for that process invention to be rejoined.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all claims to the elected product are found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowable product claim will not be rejoined. See MPEP § 821.04(b). Additionally, in order to retain the right to rejoinder in accordance with the above policy, applicant is advised that the process claims should be amended during prosecution to require the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder**. Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Priority

6. Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d).

Information Disclosure Statement

7. The information disclosure statement filed October 4, 2006 and August 10, 2005 have been considered.

Claim Rejections - 35 USC § 101

8. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

9. Claim 32 does not show the hand of man; therefore the claimed invention is directed to non-statutory subject matter. The promoter and the genetic construct are not required to encode a heterologous sequence and naturally occurring plasmids are known in the art for Bacillus strains and species that encode heat shock proteins which are known antigens (see Thorsted et al, 1999, page280, Table 2 "hsp", title, and col. 1, page 277, line 3 "promoter"); the native plasmids are genetic constructs comprise a promoter and a coding sequence for an antigen, a therapeutically active compound.

Specification

10. The disclosure is objected to because of the following: Applicant has not pointed out where in the Specification support can be found for the Amendments of paragraphs [002], [0010], [0011], [0013], [0015], [0017], [0019], new paragraph inserted between [0028-0029],

[0029], [0032-33], new paragraph inserted between [0033-0034], [0035], [0038], [0044-0045], [0052], [0054-0059].

11. The amendment of the may have introduced New Matter into the Specification.

12. For example, original paragraph [0057] positively recited that the method "comprised the step of", but has been amended to recite the tentative phrase "may involve", the scope this paragraph has been made broader. Additionally rrnO was not previously defined to encode rRNA; where is the original descriptive support for the amendment of paragraphs [0032 and 0035]?

13. Where in the instant Specification support for the amendments submitted May 29, 2007 has not pointed out and some appear to have introduced New Matter. Applicant is requested to point out where support for the amendments can be found.

Claim Objections

14. Claims 32, 34-35, 37, 39, 43-44 , 60-61 are objected to because of the following informalities:

15. Claim 32 on line three recites a semi-colon ";" additional semi-colons are recited between each of the listed compounds (i); (ii); and (iii);, the claim should be a single sentence which recites species with a comma between each and not semi-colons.

16. Claims 34-35, 37 and 39 recite the phrase "gene construct" and depend from claim 1 which recites the phrase "genetic construct". A genetic construct comprises a number of elements associated with a coding sequence that could be found in a bacterial operon. An operon in a bacteria contains a number of sequences, such as promoters, operators, regulator sequence

(cis and trans regulatory elements), SD sequences, leader /signal sequences and coding sequences. What in claim 32 is a gene construct rather than a genetic construct?

17. Claims 43-44 recites the term "is adapted"; what is the adaptation when it is encoded by the genetic construct of claim 32? No adaptations are specifically recited in claim 32 or defined in claim 43. Claim 43 is directed to a composition and not a method of use. How is the fragment of claim 44 adapted (claim 44 depending from claim 43)?

18. Claim 44 recites a non-elected invention.

19. Claims 60-61 recite the term "an antigen precursor"; how can a single antigen be multiple enzymes? Term tense is not clearly set forth in the claims.

20. Claim 33 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 33 generically defines four types of compounds of "therapeutically active compounds" two of which are claimed to be precursor antigen and precursor medicament. Precursor products are not therapeutically active until activated into the antigen or medicament. Claim 33 is broader in scope than claim 32 from which it depends which recites a therapeutically active compound. This objection can be obviated by amending claim 32 to define the compound to include precursors of antigens or medicaments.

Claim Rejections - 35 USC § 112

21. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

22. Claim 32 recites the limitation "said protein" in reference to a genetic construct. There is insufficient antecedent basis for this limitation in the claim. A genetic construct can encode a protein, nucleic acid or anti-sense nucleic acid products, therefore the phrase " said protein" lacks antecedent basis in the recitation of the term spore or genetic construct or therapeutically active compound.

23. Claim 36 recites the limitation "using a vector" in defining the claimed product of claim 32, but the product of claim 32 comprises a spore with a genetic construct and does not recite the term "vector" nor the term "genetic modification"; both terms lack antecedent basis in claim 32. There is insufficient antecedent basis for these limitations in claim 32. No specific vectors have been claimed to comprise a genetic construct and the term "genetic modification" has been deleted in claim 32.

24. Claims 45-48, and 50-53 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 44-48, 50-53 recite the phrase "the protein", but which protein does this term refer? The protein recited in paragraph (i) or the protein in paragraph (ii) ? Claim 45-46 recite the term "cell barrier" and depend from claims 37 and 32, which are compositions directed to a spore? What is the cell barrier of the spore, since a spore is a type of dehydrated cell?

25. Claim 59 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01. The omitted structural cooperative relationships are: no positively recited structure causes post-translational processing

nor are the spores required to have any specific type of secretion system ? What strains of Bacillus have type I, II and III secretion systems since the claimed spores may comprise multiple signal sequences that direct secretion in multiple ways?

Claim 59 recites phrases in "(....)" brackets and therefore does not positively recite claim limitations. The term "preferably" is recited; this does not positively set forth Applicant's invention. The term preferably is analogous to the term "such as". The invention is not distinctly claimed when claim limitation are set apart from the rest of the claim.

26. Claims 60-61 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01. The omitted structural cooperative relationships are: Claim 60-61 recites the term "biological precursors"; no specific biological precursors are provided in the spore of claims 32 or 59, therefore the enzymes would not synthesize one or more antigens. What the enzymes are that would act on the recited biological precursors are not specifically claimed based solely on a general functional characteristic.

27. Claims 65-66 and 71-73 recite the term "preferably", which is analogous to the term "such as", a term analogous to the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claim Rejections - 35 USC § 102

28. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Please Note: In light of the scope of independent claim 32 having been changed by claim amendment to no longer recite in the alternative targeting sequence or vegetative cell protein, and to recite signal sequence, vegetative cell protein of Bacillus or rRNA of the rrnO gene, the examiner will be examining Applicant's elected invention rrnO gene and signal sequence and "at least a fragment of tetanus toxin fragment C". The embodiments directed to vegetative cell protein OppA (claim 49) and cytoplasmic vegetative cell protein (claims 52-53) stand withdrawn from consideration .

29. Claims 32-37, 39-48,50-51,54,57-73 are rejected under 35 U.S.C. 102(e) as being anticipated by Goldman et al (US PG-Pub 2002/0150594, filing date December 19, 2001) in light of evidence provided by Widom (1988, abstract).

Instant claim 32, 44: Golden et al teach, describe and show the formulation of compositions that comprise Bacillus spores (see title, [005]), to include spores of Bacillus subtilis, anthracis, coagulans, globigii, stearothermophilus and thuringiensis (see [0102], col. 2, page 11)

wherein the spores comprise one or more ((see [0209]; see page 12, col. 1, paragraph 1 [0104])) genetic constructs (see [0097], [0061]))

under the control of a promoter (see [0106] "the promoters may be native, or analogous or foreign to the plant host or other type of host"; see [0107} "heterologous promoters"; see [0114 "promoter"]); see [0049 "appropriate promoter and gene fusion can be selected to control the position, amount and hence the availability of enzymatic activity or immunomodulatory or antigenic presentation on the spore"])) and further comprises

a coding sequence for a therapeutically active compound (see page 23, [0190]) the sequence encoding tetanus toxin (see page 23, [0190, middle of paragraph and bottom of paragraph "Spore systems comprising antigens or antigenic peptides associated with such diseases or toxins"]) which comprises at least the C-fragment, as tetanus toxin comprises fragments A, B and C; as well as also comprises

ribosomal RNA (rRNA see [0180]), and nucleic acid sequence that are "upstream from the start of transcription and involved in recognition and binding of RNA polymerase and other proteins to initiate transcription. A sporulation preferred promoter is a promoter capable of initiating transcription upon or during sporulation.") and therefore Bacillus subitlis spores inherently comprise rrnO in light of evidence provided by Widom (1988) that shows Bacillus subtilis to comprise rrnO promoters (see abstract, page 1747).

Instant claim 33: wherein tetanus toxin is an antigen (see page 23, [0190, middle of paragraph and bottom of paragraph "Spore systems comprising antigens or antigenic peptides associated with such diseases or toxins"]).

Instant claim 34-35: wherein the gene construct is a chimeric gene (see page 12, [0106 "chimeric gene"; page 11, [0099] "fused in frame with a nucleic acid molecule encoding a polypeptide, protein or peptide or interest, which may further be operatively linked with a nucleic acid molecule encoding a part or all of a spore coat gene" or are configured as "fusion proteins" (see [0101]) expressed in the cytoplasm or may secrete such molecules. (see [0104]).

Instant claim 36: the mother cells express the gene construct upon germination of the spores (see claim 16, page 46), wherein the vector is introduced into the bacteria (mother cell) and induced to sporulate (see [0101]); [0122].

Instant claim 37, 40-41: wherein the promoter is inducible (see "initiating transcription upon or during sporulation" or constitutive promoter (see [0114])

Instant claim 39: the gene construct has an enhancer element or upstream activator sequence (see page 10, [0097, top 1/3 of paragraph "enhancers"; [0110].

Instant claim 42: wherein the spore germinates in a human or animal body in the intestinal tract

" see [0214] Methods for administering spore systems, spore display systems, and spore encapsulate systems of the present invention include those known to those having ordinary skill in the art. Suitable routes of administration or "delivery systems" include parenteral delivery and enteral delivery, such as, for example, **oral**, transdermal, transmucosal, intravenous, subcutaneous, intramuscular, intradermal, intraperitoneal, intracapsular, intraspinal, intrastemal, intrapulmonary, intranasal, vaginal, rectal, intraocular, and intrathecal, buccal (e.g., sublingual), respiratory, topical, **ingestion**, and local delivery, such as by aerosol or transdermally, and the like. Methods for administering proteins, polypeptides, peptides, nucleic acids, and other molecules of interest to mucosal tissue via pulmonary inhalation, nasal, oral, vaginal, and/or rectal delivery are provided. The methods comprise preparing and administering to a subject a composition comprising a spore system of the present invention. Such composition may include a carrier or excipient".

Instant claim 43: elicits an immune response (see at least [0010-0012]).

Instant claim 45-46: expressed in the cell barrier (see [0014 "bound to , or contained within the spore"]; [0049 "the gene fusion can be selected to control the position, amount" of the antigenic presentation]); [0069 "expressed in multiple location on the spores"] [0068 "spore coat"] see page 10 col. 1, [0094 "encapsulated within the spore (e.g. within the outer coat, inner coat and/or cortex and/or in the core"].

Instant claim 47-48: expressed all the time in a vegetative cell ("constitutive promoter" [0114], and claim 16 "vegetative cells").

Instant claims 50-51: expressed intermittently in a vegetative cell (see [0098, the timing of expression in the life cycle of the spore" is determined by the promoter])

Instant claim 54: wherein the spore encodes the rRNA of the rrnO gene (Bacillus subtilis, inherently comprises a rrnO gene in light of evidence provided by Widom (1988, abstract) who shows Bacillus subtilis to comprise rrnO.

Instant claim 57-58: signal sequence (see page 10, [0097, top 1/3 of paragraph "signal sequence that directs secretion of an expressed protein from the host cell"] and [0094 "; local or site specific delivery of such molecules, to "outer coat, inner coat, and/or cortex and/or in the core "of the spore]; [0098 "displayed on, stored within, or expressed by the mother cell"].

Instant claim 59: secretion {see [0097 and 101] and glycosylation [0134, middle of paragraph]).

Instant claim 60-66: wherein tetanus toxin is an enzyme that is activated upon expression of the nucleic acid and activation of the link between the alpha and beta(comprises Fragment C) subunits and can be used as a pro-drug or painkiller, is a protein, and has been used as a vaccine antigen (see [0190]).

Instant claim 67, 71: at least two different spores (see claim 111).

Instant claim 68-70, 72-73: carrier (see claim 39-41).

Instant claim 71: medical condition (see [0190]).

Goldman et al inherently anticipates the instantly claimed invention, in light of evidence provided by Widom (1988, abstract), as now claimed.

1. Since the Office does not have the facilities for examining and comparing applicant's protein with the protein of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same functional characteristics of the claimed protein). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594

2. Inherently the reference anticipates the now claimed invention. Atlas Powder Co. V IRECA, 51 USPQ2d 1943, (FED Cir. 1999) states Artisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art...However, the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior arts functioning, does not render the old composition patentably new to the discoverer. The Court further held that Athis same reasoning holds true when it is not a property but an ingredient which is inherently contained in the prior art.

Conclusion

30. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Various references and US Pat/PG-Pub documents are being sited to show sequences from Bacillus and constructs for heterologous expression of antigens.

31. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (571) 272-0862. The examiner can normally be reached on flextime, but usually M-F, alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571) 272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Vgp
August 9, 2007

MARK NAVARRO
PRIMARY EXAMINER

original support for Amendments

In the specification, in relation to the paragraph numbers of the published application, US 2005/0287168 A1:

[0002] This invention relates to the germination of spores and in particular, ~~but not exclusively,~~ to spores of Bacillus species of bacteria and uses thereof.

[0010] It is an aim of the present invention to provide a spore in which said spore may be genetically modified to produce a ~~medicament~~ therapeutically active protein upon germination into a vegetative cell.

[0011] Accordingly, the present invention, provides Bacillus spores which comprise a promoter and at least one genetic construct that is under the control of the promoter and that encodes a therapeutically active compound and: a signal sequence or for said protein; a vegetative cell protein of said Bacillus; or the rRNA of the rrnO gene, wherein the spore is suitable for use in oral administration for therapeutic treatment. ~~and at least one genetic construct encoding a therapeutically active compound and a sequence or a vegetative cell protein.~~

[0013] It is a further advantage of the invention that the spores elicit an immune response at the mucosal membranes. This makes the vaccination more effective against mucosal pathogens e.g. S. typhi, V. cholera and M. tuberculosis. Thus, the antigen may be derived from a mucosal pathogen.

[0015] It is a further advantage of the present invention in that when said spore is administered to an animal, said spore germinates into a vegetative cell, said vegetative cell expresses said chimeric gene, wherein said chimeric gene ~~comprises said medicament and said protein~~encodes an antigen in order to elicit an immune response against said antigen.

[0017] Preferably the therapeutically active ~~compound~~ protein is an antigen or a medicament or a precursor to an antigen or a medicament. Preferably the gene construct is a chimeric gene. ~~Preferably the~~The spore is of Bacillus. ~~or Clostridia.~~

[0019] The gene construct may be under the control of one or more of, each or independently, an inducible promoter, ~~a promoter or~~ a strong promoter or modified promoter. The gene construct may have one or more enhancer elements or upstream activator sequences and the like associated with it.

Between [0028] and [0029], insert the following new paragraph:

--The antigen may be tetanus toxin fragment C or labile toxin B sub unit.--

[0029] The protein used may be any that are expressed only in the vegetative state. The protein may be expressed in the cell barrier or is a soluble cytoplasmic vegetative cell protein. The protein may be a protein that is expressed in the cell barrier.

[0032] The antigen may be a chimera with different vegetative cell proteins. By having the genetic construct encoding the antigen with a genetic construct encoding one or more different vegetative cell proteins it may be possible to provide a temporal expression of the antigen. For example, the ~~medicament~~ therapeutically active protein may be expressed as a chimera with a vegetative cell protein that is expressed all the time, e.g. OppA or, alternatively the rRNA of rrnO, therefore providing a constant "dose" of antigen.

[0033] Alternatively, the genetic construct encoding the antigen may be with a genetic construct encoding a vegetative cell protein that is expressed intermittently and therefore upon expression of the chimera said chimera is capable of administering the ~~medicament~~ therapeutically active protein in a time-controlled manner. The genetic construct encoding the ~~medicament~~ therapeutically active protein may also be with a genetic construct of a vegetative cell protein that is expressed initially at a high concentration but which then decreases over time, thus upon expression, the chimera is capable of administering an initial high dose of the antigen.

Between [0033] and [0034], insert the following new paragraph:

--The vegetative cell protein may be one which is expressed all the time or intermittently in the vegetative cell.--

[0035] Alternatively, the genetic construct encoding the antigen may be with a genetic construct encoding a soluble cytoplasmic vegetative cell protein~~, e.g.~~ or the rRNA from rrnO.

[0038] ~~According to a second aspect, the present invention provides a spore which is genetically modified with genetic code comprising a genetic construct encoding an antigen and a signal sequence, wherein said~~ The invention may employ a signal sequence which directs the therapeutically active protein for secretion or for post-translational processing by vegetative cells of the Bacillus. The signal sequence ~~is~~ may be adapted to target said antigen to a specific part of the vegetative cell. For example, the signal sequence may direct the medicament for secretion, for example active secretion (Type I, Type II or Type III secretion), or for post-translational processing by the vegetative cell, e.g. glycosylation.

[0044] According to a further aspect, the present invention provides spores according to the invention in which said spore ~~is genetically modified with genetic code comprising~~ comprises at least one genetic construct that is under the control of a promoter and that ~~encoding~~ encodes a ~~medicament~~ therapeutically active protein and a vegetative cell protein, as a chimeric gene.

[0045] The ~~medicament~~ therapeutically active protein may be one or more of:

[0052] According to a third aspect, the present invention provides a pharmaceutical composition for oral administration comprising Bacillus spores of the invention in association with a pharmaceutically acceptable excipient or carrier. ~~comprising a spore according to the invention in association with a pharmaceutically acceptable excipient or carrier.~~

[0054] According to a further aspect, the present invention provides ~~a composition according to the invention for use in a method of medical treatment.~~ Bacillus spores of the invention for use in the treatment of the human or animal body by therapy.

[0055] The invention also provides use of the ~~composition according to the invention in the manufacture of the medicament for use in the treatment of a medical condition.~~Bacillus spores of the invention in the manufacture of a medicament for the treatment of cholera, typhoid, tuberculosis, tetanus or E. Coli infection.

[0056] ~~A method of medical treatment would comprise treating a medical condition e.g. a disease or administering~~Medicaments may be administered as a vaccine. Medical conditions for treatment by the invention include, for example, inflammation, pain, hormonal imbalances and/or intestinal disorders.

[0057] ~~According to a further aspect, the present invention provides a method of medical treatment, which method comprises the steps of~~ Administration of medicaments of the invention may involve:

[0058] a) ~~Orally administering a spore according to the invention~~ Oral administration to a person or animal in need of medical treatment;

[0059] b) ~~Said spore~~ The spores germinating into a vegetative cell in the intestinal tract;